Total Vascular Risk as a Strong Correlate of Severity of Diabetic Peripheral Neuropathy in Nigerian Africans

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Objectives: HbA_{1c}, commonly utilised in Caucasian studies, is an inconsistent risk marker for the severity of diabetic peripheral neuropathy (DPN) severity. Other vascular risk factors have been shown to affect DPN. However, no study has examined the relative impact of HbA_{1c} and total cardiovascular risk load (TCRL) on DPN severity. Using the United Kingdom Prospective Diabetes Study cardiovascular risk engine as a measure of TCRL, we sought to determine if TCRL is a better correlate of DPN severity than HbA_{1c} alone.

Methods: We studied 277 consecutive consenting Black type 2 diabetes mellitus (DM) patients in Nigeria. We defined DPN using Michigan Neuropathy Screening Instrument thresholds defined by prior validation studies. Severity of DPN was measured using the modified Dyck's grading, which had been previously validated in Nigeria. Patients with non-diabetic causes of neuropathy were excluded.

Results: 197 (71.1%) patients had DPN. The mean HbA_{1c} value was 6.9%. The HbA_{1c} correlated significantly to the fasting plasma glucose (r=.36), but did not correlate significantly to the DPN severity (P=.304, rho=.075). The TCRL had the strongest significant correlation to DPN severity (P=<.001, rho=.285). Age and dyslipidemia, which are also components of the TCRL, emerged as independent statistical predictors of DPN severity in multivariate analysis.

Conclusions: In Nigerian Africans, TCRL was a stronger statistical correlate of DPN severity than HbA_{1c}. In the setting of multiracial studies, the development of a special risk engine for monitoring the risk of DPN is recommended as a substitute for HbA_{1c} alone. (*Ethn Dis*. 2012; 22(1):106–112)

Key Words: Diabetic Peripheral Neuropathy, HbA_{1c}, Peripheral Neuropathy, Risk Factors

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Introduction

The neglected epidemic of cardiovascular diseases is currently ravaging low and medium income countries.[1,2] This silent epidemic includes diabetes mellitus (DM), which is the leading cause of neuropathy globally.[3,4] Diabetic peripheral neuropathy (DPN) is the most common late complication of DM, and some of its consequences include pain, falls, foot ulceration, amputation, sleep impairment, depression and impaired quality of life.[5–7] Unfortunately, to date, the pathogenesis of DPN is poorly understood and there is no effective treatment.[8,9]

Furthermore, a consistent and comprehensive modifiable risk marker for DPN severity is lacking.[10] Until now, in Caucasian studies, chronic hyperglycemia measured by HbA_{1c} has been utilized.[11,12] However, it is neither a consistent marker of DPN occurrence nor its severity.[10,13–15] For instance, although the Diabetes Control Complications Trial (DCCT) reported a significant reduction in neuropathy in the intensively treated groups (with lower HbA_{1c}),[14] the Veterans Affairs Diabetes Trial, observed a non-significant increase in autonomic neuropathy in the intensive-therapy group (with lower HbA_{1c}).[13] In the Veterans Affairs Diabetes Trial, and a recent Swedish study,[16] HbA_{1c} had no significant effect on DPN.[13] Also in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus, a 2.07% reduction in HbA_{1c} had no significant impact on diabetic peripheral or autonomic neuropathy.[17]

Recent studies have shown that vascular risk factors apart from hyperglycemia are involved in its progression.[13,18] The pathogenesis of DPN is complex and multifactorial.[8,9] Therefore, it is desirable to have an aggregate (multifactorial) risk marker as its composite monitor. No study had examined the relationship between total cardiovascular risk load (TCRL) and the severity of DPN. We sought to use the United Kingdom Prospective Diabetes Study (UKPDS) cardiovascular risk engines, which includes ethnicity and other vascular risk factors, to fill this void.[10,19–21] Secondly, we are not aware of any study that has determined the relative impact of TCRL versus isolated HbA_{1c} on DPN severity. Earlier models by Dyck did not include other vascular risk factors apart from markers of chronic glycemic exposure.[22] We, therefore, sought to determine the relative effect of chronic hyperglycemia (measured by the HbA_{1c}) vs TCRL (measured by the UKPDS cardiovascular risk engines) on DPN severity in Nigerian Africans.[14]

Methods

Setting and Patients

Based on the American Diabetic Association criteria, we recruited all consecutive consenting patients with type 2 DM[23] (T2DM) attending the medical outpatient clinic of the University College Hospital (UCH) Ibadan, Nigeria,

We sought to determine the relative effect of chronic hyperglycemia vs TCRL (total cardiovascular risk load) on DPN severity in Nigerian Africans.[14]

between February 2008 and March 2009. Ethical approval was obtained from the Joint Ethical Committee of the UCH and University of Ibadan.

A total of 344 T2DM patients were seen during the study period. Persons with suspected hereditary neuropathy, those on medications known to cause peripheral neuropathy and those with positive human immunodeficiency virus (2 patients) or Venereal Disease Research Laboratory serology were excluded. Forty-five persons who declined phlebotomy for HbA_{1c} estimation, and 20 who did not give consent were also excluded, resulting in 277 patients finally participating in the study.

Clinical Assessment

Sociodemographic data was obtained as well as clinical information on cardiovascular risk factors required for the computation of the UKPDS risk score for coronary heart disease and stroke.[19–21] The medical history included the duration of DM as well as personal and family history of cardiovascular risk factors including hypertension, ischemic heart disease, cerebrovascular disease and peripheral vascular disease. History of cigarette smoking and alcohol use was also obtained. The radial pulse was examined in all patients. Blood pressure was measured using standard techniques and hypertension was diagnosed if blood pressure was ≥140/90 mm Hg[24] or if patients were on drug treatment for previously diagnosed hypertension.

Presence of neuropathy was determined using the Michigan Neuropathy Screening Instrument (MNSI), a validated instrument for identification of symptoms and signs of DPN.[14,25] It consists of a 15-item questionnaire and a structured examination that jointly samples symptoms of small and large fiber neuropathies and their complications. The questionnaire inquires about positive (pain, temperature sensation, tingling) and negative (numbness) sensory symptoms, cramps and muscle weakness, foots ulcers or cracks, amputation, and prior diagnoses of diabetic neuropathy by a physician. Neuropathic signs were assessed using the MNSI examination, a structured assessment including inspection of the feet, and evaluation of ankle reflexes, vibration and touch sensation. We used a 128 Hz tuning fork to assess vibration sense and a 10g filament to assess touch. A Queen Square tendon hammer was used to test for deep tendon reflexes. The MNSI score was determined using the MNSI manual.[14] Neuropathy was defined operationally as ≥7 positive responses on the MNSI questionnaire or a score >2.0 on the MNSI examination, thresholds stipulated by prior validation studies.[14] The criterion for a positive MNSI examination, the most objective component of the MNSI, was established to achieve high specificity (95%) and sensitivity (80%), with a positive predictive value of 97% and a negative predictive value of 74%[14] when validated against the San Antonio consensus criteria.[26] As utilized in the DCCT trial involving 1441 patients, the MNSI permits us to establish the presence or absence of neuropathy though it has not been validated as a measure of neuropathy severity.[14,27–29]

We, therefore, used modified Dyck's grading, previously validated in Nigeria,[27] to assess severity of DPN among those with DPN. Grade 0 denotes no symptoms but a sign of neuropathy, grade 1 is ≥2 abnormal neurological tests, grade 2 for ≥2 abnormal tests plus symptoms, while grade 3 is ≥2 abnormal tests plus debilitating symptoms.[27]

Laboratory Tests

Samples were taken for laboratory analysis during recruitment. In addition, retrospective data on fasting plasma glucose (FPG) was obtained from the hospital records. We used HbA_{1c} and a mean of three consecutive FPG estimations to assess glycemic control. Patient blood samples were taken, after an overnight fast of 8–14 hours, for FPG, fasting lipid profile and glycated hemoglobin analysis. We assessed FPG using the glucose oxidase enzymatic method while total cholesterol and triglycerides were analyzed using enzymatic methods with values read off a colorimeter. High-density lipoprotein cholesterol (HDL-C) was determined using selective precipitation; followed by enzymatic method for measuring cholesterol. Calculated values for low-density lipoprotein cholesterol (LDL-C) were obtained using the Friedewald equation (the plasma triglycerides were not >400mg/dL).[30]

The HbA_{1c} samples were stored at 2–8C. Analysis was done within one week of storage using the HbA_{1c} ionic exchange chromatographic method (DIALAB, Austria). The following formula given by the manufacturer of the kit was used to obtain DCCT referenced values: HbA_{1c} (NGSP) (%) = .86 HbA1c- Dialab (%) + .24.

We did not assess for parallel markers of microangiopathic complications because our focus was to seek the relationship between TCRL and DPN in comparison to HbA_{1c} and DPN.

Statistical Analysis

A validated diabetes specific risk calculator known as UKPDS Risk Engine was used to calculate the absolute cardiovascular risk. It was developed following a randomized controlled trial involving 5,102 patients with T2DM who were followed up for 20 years and has been found to be superior to other previously used risk engines in persons with diabetes.[19,20] It provides equations for absolute risk, incorporating the effect of multiple risk factors to give overall event rates, rather than relative risk.[19,20]

Age, sex, ethnicity, smoking status, presence or absence of atrial fibrillation, duration of diabetes, HbA_{1c}, cigarette smoking, systolic blood pressure, total cholesterol and HDL-cholesterol were utilised for the automatic computation of the UKPDS risks of all coronary heart disease (CHD), fatal coronary heart disease (FATCHD), all stroke, and fatal stroke.[21] This was done using UKPDS

Table 1. Diabetic peripheral neuropathy (DPN) severity strata by UKPDS-CHD risk score

Severity of DPN	*N*=197 *n*, %	UKPDS-CHD[a] median score (IQR)	UKPDS FATCHD[b] median score (IQR)
Grade 0	6, 3.0	3.0 (1.1–3.9)	1.5 (.5–2.1)
Grade 1	32, 16.2	3.3 (1.7–6.4)	1.5 (.7–3.8)
Grade 2	87, 44.2	5.2 (2.8–10.2)	3.2 (1.4–7.5)
Grade 3	72, 36.6	6.8 (4.4–10.1)	4.2 (2.5–7.2)
K-W χ^2		16.35	17.19
K-W *P*		.001	.001

IQR, Interquartile range; K-W, Kruskal Wallis; UKPDS, United Kingdom Prospective Diabetes Study.
[a] UKPDS risk score for coronary heart disease.
[b] UKPDS risk score for fatal coronary heart disease.
In spite of overlaps, the first and third quartile values of CHD and FATCHD progressively increased from Dyck grade 0 to Dyck grade 3.

Risk Engine software,[21] into which the models have been incorporated. It generates an estimate of the risk of development of cardiovascular disease in the following 10 years. According to the model, patients could be classified into the following sub-groups: low risk (0%–15%), moderate risk (15%–30%) and high risk (>30%).

Bivariate relationship between DPN severity and its potential determinants were sought using chi-square and Spearman rank's correlation statistics. Stepwise regression was used for the multivariate analysis. We included variables with significant bivariate relationship to DPN severity (Tables 2 and 3) in the regression model. Variables with high collinearity were excluded. Data analysis was carried out using the SPSS software; significance was set at $P<.05$.

RESULTS

We assessed 277 Black Nigerian patients (111 males, 40.1%); 197 (71.1%) of them had DPN. The mean age (SD) of the study participants was 60.0 (10.0) years while the mean BMI (SD) was 26.3 (4.9) kg/m^2. Dyslipidemia was present with mean values of 101.2 (37.0) and 35.5 (9.6) mg/dL for LDL-c and HDL-c respectively. The mean duration of diabetes mellitus was 7.7 years while the mean (SD) HbA_{1c} % was 6.9 (2.0). The mean (SD) systolic blood pressure was 139 (25) mm Hg.

Family history of DM was present in 92 patients (33.2%) while 107 (38.6%) had consumed alcohol but only 15% had ever smoked cigarettes. Nearly 71% of the patients were on oral glucose lowering agents (OGLA) while 18.5% were on insulin, 3.7% on dietary therapy alone and 6.9% on both OGLA and insulin. A history of unilateral and bilateral foot ulceration was present in 5.8% and 1.5% of the population, respectively, while 2.5% had had a lower limb amputation.

The stratification of DPN severity in those with DPN is shown in Table 1 in relation to the median TCRL (as measured by UKPDS) for each strata. Using the Kruskal-Wallis test, there was significant difference in TCRL among DPN severity strata ($P=.001$, Table 1 and Figure 1). Sex had no significant impact on DPN severity, ($\chi^2=1.439$, $P=.487$). The relationship of other demographic and clinical variables to DPN severity is presented in Table 2. Only age, average fasting plasma glucose, systolic blood pressure, pulse pressure, LDL-cholesterol, LDL/HDL ratio and all UKPDS risk scores correlated significantly to DPN severity. The UKPDS-FATCHD had the strongest significant correlation to DPN severity (rho =.285, $P<.00001$) Conversely, HbA_{1c}, which correlated significantly to the FPG at contact ($P<.0000000001$, $r=.37$) and average FPG ($P<.0000000001$, $r=.36$), did not correlate significantly to DPN severity (rho=.075, $P=.304$ Table 2 and Figure 1). The HbA_{1c}, however, correlated significantly to UKPDS risk score for coronary heart diseases ($P=.003$, $r=.179$) and UKPDS risk score for fatal coronary heart diseases ($P=.001$, $r=.197$) of which it is a component.

In the regression analysis, age and LDL/HDL, both components of the UKPDS risk scores, were significant predictors of DPN severity (table 3).

DISCUSSION

Diabetic peripheral neuropathy is very common in T2DM patients. We

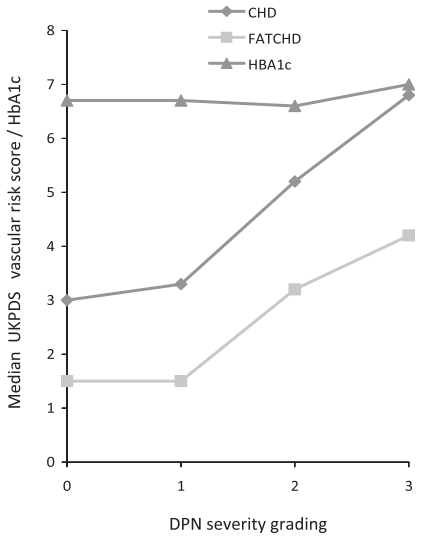

Fig 1. Median vascular risk score by DPN severity. CHD, UKPDS risk score for coronary heart disease. FATCHD, UKPDS risk score for fatal coronary heart disease

Table 2. Correlations of clinical and laboratory parameters to severity of diabetic peripheral neuropathy

Parameter	Spearman rank ρ	*P*
Age	.200	.005
DM duration	.129	.076
HbA_{1c} × duration of DM	.142	.051
Hypertension duration	.116	.172
Systolic blood pressure × duration of hypertension	.129	.131
Height	.074	.309
Weight	.048	.505
BMI	.012	.872
Systolic blood pressure	.184	.011
Diastolic blood pressure	.050	.494
Pulse pressure	.173	.017
HbA_{1c}	.075	.304
Fasting plasma glucose 1st prior visit	.064	.445
Fasting plasma glucose 2nd prior visit	.116	.173
Fasting plasma glucose at contact	.116	.112
Average of 3 fasting plasma glucose	.155	.032
Total cholesterol	.118	.105
Triglycerides	.003	.965
LDL-cholesterol	.144	.048
HDL-cholesterol	−.073	.316
LDL-C/HDL-C	.179	.014
UKPDS risk score for coronary heart disease (CHD)	.276	.000
UKPDS risk score for fatal coronary heart disease (FATCHD)	.285	.000
UKPDS risk score for stroke	.236	.001
UKPDS risk score for fatal stroke	.253	.000

DM, diabetes mellitus; BMI, body mass index; UKPDS, United Kingdom Prospective Diabetes Study

found DPN in 71.1% of the study patients, which was similar to the 75% rate previously documented in Jos, Nigeria.[27] It is a major risk factor for the development of foot ulceration, and increased morbidity and mortality.[18,31] It is also a surrogate marker for other microangiopathic complications (nephropathy, retinopathy).[4] Hence it deserves adequate focus to elucidate its risk markers.

Although previous studies have reported the impact of individual cardiovascular risk factors on DPN and DPN severity, this is the first study to determine the relative impact of TCRL vs HbA_{1c} alone on DPN severity. In most Caucasian studies, much attention had been given to the intensity of glycemic control measured by HbA_{1c}, whose concentration is directly proportional to the mean concentration of blood glucose in the preceding 8–12 weeks. In this study, HbA_{1c} correlated significantly with the average FPG but demonstrated no significant impact on DPN severity. This may be due to the lower[32] mean HbA_{1c} level (6.9%) relative to other studies that reported such impact (7.4 to 9.1%).[27] The mean value of 6.9% in our study is identical to that of the intensive treatment group in the Veterans Affairs Diabetes Trial and is indicative of better glycemic control.[13] This may suggest that with good glycemic control, other vascular risk factors (including ethnicity) may become more important in the pathogenesis and progression of DPN. Multiracial studies are required to confirm this.

However, in a broader sense, in consonance with our observation, even in the Veterans Affairs Diabetes Trial,[13] Veterans Affairs Cooperative Study in T2DM,[17] and a recent Swedish study,[16] HbA_{1c} had no significant impact on DPN. Therefore, updated mean HbA_{1c} has been suggested by some authors.[33,34]

Table 3. Stepwise multiple regression model predicting diabetic peripheral neuropathy (DPN) severity[a]

Statistical predictor	*t*	*P*	Beta	Standardized beta
Age	3.047	.0003	.015	.214
LDL/HDL	2.896	.0004	.121	.204
UKPDS risk scores	2.789	.0006	.923	

[a] Candidate independent variables tested were those with significant correlation to DPN severity (age, average FPG, SBP, UKPDS fatal CHD, LDL-c/HDL-C). Significant variables for the model (R=.292, R^2=.085, P<.0001) are shown.

This study suggests that total cardiovascular risk load is a stronger correlate of clinically defined DPN severity than isolated HbA_{1c} (Figure 1).[11,18,22,46]

Although it has been reported to be more useful, it does not incorporate glycemic fluctuations, a factor which has also been linked to DPN.[34,35]

Furthermore, as published in the Swedish study, we observed no relationship between DPN severity and reported duration of chronic glycemic exposure.[16] The impact of diabetes duration reported in other studies[36] may be due, at least in part, to the contributory effect of age.[36] In a study of endoneurial capillary densities, no correlation was found between HbA_{1c} or duration of DM and neuropathic severity or capillary pathology.[37,38] However, in keeping with the vascular hypothesis, all measures of nerve capillary pathology correlated significantly with neurophysiological and neuropathological measures of neuropathic severity.[37]

Therefore, the results of this study, buttressed by the findings of the Veterans Affairs Diabetes Trial[13] and many other studies[8,15–17,37,39–42] suggests that hyperglycemic-based metabolic hypothesis alone is insufficient to account for DPN.[11,22,43,44] This may have implications for agents targeting the metabolic mediators of DPN. Many of these agents, which showed promise in animal experiments, have failed in clinical trials.[8,9,45]

Conversely, the observed relationship between TCRL and DPN severity in this study supports the vascular-hypoxic hypothesis whereby endoneurial microvascular damage results in neuropathy.[11,22,43,44] Although, individual vascular risk factors such as age, LDL cholesterol, systolic blood pressure, pulse pressure, and average fasting plasma glucose were significantly correlated with DPN severity, TCRL had the strongest correlation to DPN severity. It is perhaps the synergistic effect of these vascular factors aggregated in the UKPDS cardiovascular risk engine that results in DPN. Even though HbA_{1c} has been associated with neural vascular injury, other risk factors aggregated in the risk engine may be equally if not more important, particularly when the HbA_{1c} is near normal.[46] The association of DPN with markers of macroangiopathy[16] coupled with the alterations of endoneurial capillaries have indicated a strong role for vascular risk factors in DPN neuropathy.[4]

Of these circulatory factors, age and LDL/HDL-cholesterol ratio were the most prominent in the regression model. Age is a potent non-modifiable vascular risk factor whose association with DPN has been reported in many studies,[8,9,22,36] while dyslipidemia has also been found to be associated with DPN by various workers.[16,18,27,47] Dyslipidemia and other vascular risk factors including, body mass index, smoking, and hypertension[15] reported in the large-scale EURODIAB and other studies are potentially modifiable.[17–19] These factors have also been associated with other microangiopathic complications.[48] These findings suggest that modification of TCRL may play a major role in reducing DPN severity. However, more prospective and larger studies as well as interventional studies aimed at reducing TCRL are required to conclusively establish this. The impact of ethnicity, a component of the UKPDS cardiovascular risk engine, should also be explored further in multiracial studies.

Limitations and Future Directions

Although other microangiopathic complications are well-correlated with DPN, we did not specifically assess for other microangiopathic and macroangiopathic complications in our patients. It would be interesting to study the interrelationships among these complications as well as the impact of TCRL on their emergence and severity.

Although the combination of clinical, neurophysiological and histological[32] assessment gives the most accurate grading, clinical grading scales such as was used in this study[27,36] are valid, simpler, time-saving, cheaper, non-invasive and best suited for routine clinical use.[36,49,50] Therefore, studies using routine clinical parameters may have greater clinical implications and universal applicability particularly in resource-poor settings.[51] Furthermore, our results are corroborated by studies using neurophysiological and neuropathological measures of DPN in which no correlation was found with HbA_{1c}.[8,15–17,37,39–42]

The low R^2 found in this study, implying a huge residual unexplained variation by the regression model, is uniformly reported in many previous studies[10,22,32] regardless of the inclusion of parallel microangiopathic markers. For instance, a R^2 of .113 was found in a study using morphologic grading and parallel microangiopathic markers.[10,32] It portends that there are still unmeasured factors driving the progression of DPN.[10]

Thus, beyond hyperglycemia, and parallel markers of microangiopathy such as retinopathy and nephropathy,[22] there are probably many putative and yet-to-be-identified factors[5,10,52] that need to be elucidated and controlled in future exploratory and interventional studies.[8–10,45]

Implications

This study suggests that total cardiovascular risk load is a stronger correlate of clinically defined DPN severity than isolated HbA_{1c} (Figure 1).[11,18,22,46] Furthermore, age and dyslipidemia, both of which are components of the TCRL, are independent statistical predictors of DPN severity.[16,41,47] Dyslipidemia is

modifiable and may be a worthy target to prevent DPN progression, as suggested by other studies.[16,41,47]

The outstanding relationship of DPN severity to UKPDS risk engine designed originally for predicting macrovascular complications (stroke and coronary artery disease), suggests that both microangiopathic and macroangiopathic complications may have similar underlying pathological mechanisms.[16] The stronger association between the TCRL and DPN severity suggests that TCRL is more important than hyperglycemia alone in the management of DPN. In the setting of a multiracial study, the development of a special automated aggregate risk engine for monitoring the risk of DPN is recommended as a substitute for HbA_{1c} alone.

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Manuscript draft: Owolabi, Ipadeola
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